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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/712,363	11/12/2003	Elliott P. Dawson	13744-2	1313

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EXAMINER	
BERTAGNA, ANGELA MARIE	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 08/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/712,363	DAWSON, ELLIOTT P.	
	Examiner	Art Unit	
	Angela Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *11-22 and 27-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-10 and 23-25* is/are rejected.

7)☒ Claim(s) *1-10 and 23-26* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 1/19/2004; 1/22/2004
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-10, 23-26 and SEQ ID Nos: 9, 10, 15, 16, 25, 26 and the 1522 C->T polymorphism in SEQ ID No: 1, in the reply filed on June 14, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 11-22 and 27-29, SEQ ID Nos: 3 (including variant forms cited in claim 28), 11-14, 17-24, 27-32, and the non-elected variants of SEQ ID No: 1 recited in claim 26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on June 14, 2006.

Priority

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35

U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Provisional Application No. 60/306,675 (filed 7/20/2001), fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. This provisional application teaches general screening the CYP2D6 gene for polymorphic sequences, but does not recite any specific sequences detected or primer set(s) used in the screening process. Regarding claims 1-10 and 23-25, the provisional application fails to teach the specific primer sets recited in these claims. Also, the provisional application fails to teach the polymorphic variant of SEQ ID No: 1 in claim 26. Therefore, the instant claims 1-10 and 23-26 have only been granted benefit of the filing date of non-provisional application 10/360,790, filed July 18, 2002.

Claim Objections

3. Claims 1-10 and 23-26 are objected to because of the following informalities: These claims recite non-elected SEQ ID Nos: and variant sequences. Appropriate correction is required.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1, 2, 4-9 and 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cronin et al. (USPN 6,027,880) in view of GenBank Accession No. M33388 (1994) and further in view of Buck et al. (Biotechniques (1999) 27: 528-536).

Cronin teaches arrays of immobilized probes for simultaneously detecting multiple mutations in the CYP2D6 gene (see abstract).

Regarding claim 1, Cronin teaches that primers may be designed based on the known CYP2D6 gene (and its different alleles) to amplify target sequences by multiplex PCR for subsequent detection of sequence variations (see column 43, line 35 – column 44, line 60 and column 35, lines 44-48). Specifically, Cronin states, "For analysis of mutants through all or much of a gene, it is often desirable to amplify several segments from several paired primers. The different segments may be amplified, sequentially or simultaneously by multiplex PCR. Frequently, fifteen or more segments of a gene are simultaneously amplified by PCR (column 44, lines 49-55)." Cronin also states, "Paired primers are selected to flank the borders of a target polynucleotide of interest. More than one target can be simultaneously amplified by multiplex PCR in which multiple paired primers are employed (column 35, lines 44-48)."

Regarding claim 2, Cronin teaches that multiple primer pairs (up to 15) may be employed in the multiplex amplification method (column 14, lines 49-55).

Regarding claims 4-8, Cronin teaches primers containing 21 nucleotides (see Table 6, col. 43/44, where the CYP-PCR8-F and CYP-PCR9-R primers are 21 nt in length).

Regarding claim 9, Cronin teaches that the primers may further include a tail sequence (column 58, lines 15-34, where primers containing a 5' RNA polymerase promoter sequence are taught).

Regarding claim 23, Cronin teaches a kit for screening a polynucleotide sample to detect and identify the presence of one or more than one variant in the CYP2D6 gene in the sample, comprising suitable amounts of a primer set (see column 43, line 35 – column 44, line 60 and column 35, lines 44-48).

Regarding claims 24 and 25, Cronin teaches that the kit further includes additional reagents to amplify the sample, such as DNA polymerase and buffers (see, for example, column 56, lines 50-56, where PCR reaction conditions are taught).

Cronin does not teach primers consisting of 16 or more consecutive nucleotides of the instant SEQ ID Nos: 9, 10, 15, 16, 25, or 26.

GenBank Accession No. M33388 teaches the sequence of the human CYP2D6 gene. The instantly claimed primer sequences are all found in this gene sequence. SEQ ID Nos: 9, 10, 15, 25, and 26 may be matched exactly to the gene sequence or its complementary sequence (see alignments below).

SEQ ID NO: 9

```
RESULT 32
HUMCYP2D6
LOCUS       HUMCYP2D6               9432 bp    DNA     linear   PRI 22-NOV-
1994
DEFINITION  Human cytochrome P450 IID6 (CYP2D6) gene, complete cds.
ACCESSION   M33388
VERSION     M33388.1  GI:181303
KEYWORDS    cytochrome P450; cytochrome P450 IID6.
SOURCE      Homo sapiens (human)

Qy          1 AGCAGAGGGCAAAGGCCATCA 21
              |||||||||||||||||||||
Db       1472 AGCAGAGGGCAAAGGCCATCA 1492
```

SEQ ID No: 10

```
RESULT 31
HUMCYP2D6/c
LOCUS       HUMCYP2D6               9432 bp    DNA     linear   PRI 22-NOV-
1994
DEFINITION  Human cytochrome P450 IID6 (CYP2D6) gene, complete cds.
ACCESSION   M33388
VERSION     M33388.1  GI:181303
KEYWORDS    cytochrome P450; cytochrome P450 IID6.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens

Qy          1 CTCTCTGCCCAGCTCGGACTA 21
              ||||||||||||||||||||
Db       2752 CTCTCTGCCCAGCTCGGACTA 2732
```

SEQ ID No: 15

```
RESULT 33
HUMCYP2D6
LOCUS       HUMCYP2D6               9432 bp    DNA     linear   PRI 22-NOV-
1994
DEFINITION  Human cytochrome P450 IID6 (CYP2D6) gene, complete cds.
ACCESSION   M33388
VERSION     M33388.1  GI:181303
KEYWORDS    cytochrome P450; cytochrome P450 IID6.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
Qy          1 TGGTGGGGCTAATGCCTTCAT 21
              ||||||||||||||||||||
Db       3173 TGGTGGGGCTAATGCCTTCAT 3193
```

SEQ ID No: 25

```
RESULT 30
HUMCYP2D6
LOCUS       HUMCYP2D6               9432 bp    DNA     linear   PRI 22-NOV-
1994
DEFINITION  Human cytochrome P450 IID6 (CYP2D6) gene, complete cds.
ACCESSION   M33388
VERSION     M33388.1  GI:181303
KEYWORDS    cytochrome P450; cytochrome P450 IID6.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens

Qy          1 GGAGGCAAGAAGGAGTGTCAG 21
              ||||||||||||||||||||
Db       4705 GGAGGCAAGAAGGAGTGTCAG 4725
```

SEQ ID No: 26

```
RESULT 19
HUMCYP2D6/c
LOCUS       HUMCYP2D6               9432 bp    DNA     linear   PRI 22-NOV-
1994
DEFINITION  Human cytochrome P450 IID6 (CYP2D6) gene, complete cds.
ACCESSION   M33388
VERSION     M33388.1  GI:181303
KEYWORDS    cytochrome P450; cytochrome P450 IID6.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens


Qy          1 ACCAATCTGGGCAGTCAGAGT 21
              |||||||||||||||||||||
Db       6101 ACCAATCTGGGCAGTCAGAGT 6081
```

Buck analyzed the effect of primer design strategy on the performance of DNA sequencing primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that every single primer worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, every single control primer functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95

control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to design any set of primer pairs from the known CYP2D6 gene sequence. Cronin taught several primer pairs designed from the known CYP2D6 gene (see Table 6. col. 43/44) and further taught that these primer pairs were useful for multiplex amplification of specific CYP2D6 target sequences (see column 43, line 35 – column 44, line 60 and column 35, lines 44-48). The teachings of Buck, that all primer sequences were essentially equivalent, would have further motivated the person of ordinary skill to design any amplification primer designed from the known sequence of the CYP2D6 gene with a reasonable level of success. Absent any secondary considerations, the instantly claimed primer pairs cannot be considered to be non-obvious in light of the teachings of Cronin, GenBank Accession No. M33388, and Buck.

Attention is also directed to the court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995) where the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties".

As noted above, the CYP2D6 gene sequence was well known in the art as demonstrated by GenBank Accession No. M33388. Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for amplification primers, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

6. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cronin et al. (USPN 6,027,880) in view of GenBank Accession No. M33388 (1994) and further in view of Buck et al. (Biotechniques (1999) 27: 528-536) and further in view of Longo et al. (Gene (1990) 93(1): 125-128).

The teachings of Cronin, GenBank Accession No. M33388, and Buck have been discussed above.

None of the above references teaches primers containing UTP substituted for TTP.

Longo teaches a method of eliminating carry-over contamination in PCR. Longo teaches that primers containing a uracil substitution for thymine will generate products susceptible to degradation by uracil DNA glycosylase (see abstract). Specifically, Longo states, "We report that carry-over contamination can be controlled by the following two steps: (i) incorporating dUTP in all PCR products (by substituting dUTP for dTTP, or by incorporating uracil during synthesis of the oligodeoxyribonucleotide primers; and (ii) treating all subsequent fully preassembled starting reactions with uracil DNA glycosylase (UDG), followed by thermal inactivation of UDG....Because UDG does not react with dUTP, and is also inactivated by heat

denaturation prior to the actual PCR, carry-over contamination of PCRs can be controlled effectively if the contaminants contain uracils in place of thymines (abstract)."

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to substitute at least one thymine in the primers of Cronin with uracil, since Longo taught that uracil substitution enabled the user to eliminate carry-over contamination in subsequent amplification reactions through the action of UDG (see above). The ordinary practitioner would have been motivated to design uracil-substituted primers in order to minimize carry-over contamination in subsequent PCR amplifications, as taught by Longo, and thereby improve the accuracy of the results by elimination of false positives. Since Longo taught that the uracil substitution could be incorporated during primer synthesis, the person of ordinary skill would have expected a reasonable level of success in applying the teachings of Longo to the chemically synthesized primers of Cronin. Therefore, the ordinary user of the primers of Cronin, interested in minimizing carry-over contamination in subsequent PCR amplifications, would have been motivated to incorporate at least one uracil base for thymine as suggested by Longo, thus resulting in the instantly claimed invention.

Allowable Subject Matter

The following is a statement of reasons for the indication of allowable subject matter: The prior art does not teach or suggest the polymorphic variant of SEQ ID No: 1 where the cytosine at position 1522 is replaced with a thymine (claim 26). Also, the prior art does not teach or suggest SEQ ID No: 16. The closest prior art (GenBank Accession No. M33388 cited above) teaches a sequence with a single mismatch to SEQ ID NO: 16.

Conclusion

No claims are currently allowable. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Guida et al. (US 2003/0170651 A1), Risinger et al. (US 2003/0044797 A1), and Milos et al. (US 2003/0083485 A1) teach multiplex amplification of the CYP2D6 gene.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela Bertagna whose telephone number is (571) 272-8291. The examiner can normally be reached on M-F 7:30-5 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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JEFFREY FREDMAN
PRIMARY EXAMINER
9/16/08